Remarks:

In the Office Action dated February 6, 2006, claims 1-19, in the above-identified U.S. patent application were rejected. Reconsideration of the rejections is respectfully requested in view of the above amendments and the following remarks. Claims 1-19 remain in this application.

Claims 1-9 and 16-19 were rejected under 35 USC §112, second paragraph as lacking enablement. The claims have been amended to indicate that the tumors are urokinase associated malignant tumors. Since page 3 of the office action acknowledges that the specification is enabling for treating urokinase associated disorders, applicants request that this rejection be withdrawn.

Claims 1-3, 5, 8-12, 15 and 18-19 were rejected under 35 USC §103(a) as unpatentable over Xing in view of Pentapharm 1998 or Pentapharm 1997. Applicants respectfully contend that at best it would have been obvious to try various urokinase inhibitors as a treatment for tumors since several were shown not to be useful as pharmaceutical agents. In other words, the prior art may indicate that it is desirable to find a urokinase inhibitor which can be used to treat tumors but the cited prior art does not indicate which urokinase inhibitors will work *in vivo* for treating tumors. The Federal Circuit found in *Merck & Co. V. Biocraft Labs.*, 874 F.2d 804 (Fed. Cir. 1989) that prior art that makes the invention only obvious to try rather than obvious gives either no indication of which parameters are critical or no direction as to which of many possible choices is likely to be successful. In *In re Merck & Co.*, 800 F.2d 1091 (Fed. Cir.

1986), the court indicated that the correct standard is whether one skilled in the art would have a reasonable expectation that the beneficial result will be achieved. In *Hybritech Inc. v. Monoclonal Antibodies, Inc.*, 802 F.2d 1367 (Fed.Cir. 1986), the prior art showed sandwich assays using polyclonal antibodies. This prior art was combined with other references which showed that monoclonal antibodies could be produced in large quantities. The court held that the claims were not obvious but only obvious to try since the combination of prior art did not suggest how the end might be accomplished. In the present situation, Xing discloses only urokinase inhibitor B-428 as an antitumor agent and does not suggest that any and all urokinase inhibitors are useful as antitumor agents. Though other prior art may suggest that a urokinase inhibitor antitumor agent is desirable, none of the cited or submitted prior art indicates how such an agent can be identified. Several of the submitted references indicate that *in vitro* activity is not a reliable predictor of *in vivo* results. In view of this, the present invention is not obvious, only obvious to try in view of the prior art.

As pointed out in earlier responses, the Pentapharm catalogue discloses only research agents not pharmaceutical compounds. Attached to this response is a declaration signed by the manager of the legal department of Pentapharm indicating that Pefabloc was sold only for research purposes in the 1997 and 1998 catalogs. One skilled in the art would not reasonably believe that a research agent would have *in vivo* activity in view of the previously submitted references which show that not all urokinase inhibitors are useful as pharmaceutical agents despite their *in vitro* activity. An effective pharmaceutical

compound must be shown to have no cytotoxicity, must be taken up by the organism and must have efficacy. The present application shows that the L-enantiomer of Nα(2,4,6-Triisopropylphenylsulfonyl)-3-amidino-(D,L)-phenylalanine 4-ethoxycarbonylpiperazide has these properties. The Pentapharm catalogs show only that this compound is a low molecular weight synthetic inhibitor which inhibits urokinase *in vitro*. There is no suggestion that Nα(2,4,6-Triisopropylphenylsulfonyl)-3-amidino-(D,L)-phenylalanine 4-ethoxycarbonylpiperazide has efficacy *in vivo*, has no cytotoxicity *in vivo* and is taken up by the organism. Xing does not cure this deficiency because Xing discloses only urokinase inhibitor B-428 as an antitumor agent and does not suggest that Nα(2,4,6-Triisopropylphenylsulfonyl)-3-amidino-(D,L)-phenylalanine 4-ethoxycarbonylpiperazide is useful as an antitumor agent. As pointed out on page 5 of the office action "the pharmaceutical art is unpredictable, requiring each embodiment to be individually assessed for physiological activity" and "Moreover, it is known that repeated therapeutic failures, after promising in vitro results, suggest to the skilled artisan that claims based on in-vitro data. directed to treating cancers or tumors generally, are highly unpredictable, as taught by Trisha Gura's article in *Science*, November 1997". In view of this unpredictability, applicants contend that one skilled in the art would not reasonably believe that Nα(2,4,6-Triisopropylphenylsulfonyl)-3-amidino-(D,L)-phenylalanine 4-ethoxycarbonylpiperazide would be useful as a pharmaceutical compound in view of its disclosure as a research reagent in the Pentapharm catalogues and

the disclosure of an unrelated urokinase inhibitor in Xing. In view of the above discussion, applicants request that this rejection be withdrawn.

Claim 4 was rejected under 35 USC §103(a) as unpatentable over Xing in view of Pentapharm 1998 or Pentapharm 1997 further in view of DeVita. DeVita is cited for the disclosure that carcinomas frequently spread and grow in the lymphatic system. DeVita does not suggest or disclose that Nα(2,4,6-Triisopropylphenylsulfonyl)-3-amidino-(D,L)-phenylalanine 4-ethoxycarbonylpiperazide has efficacy *in vivo*, has no cytotoxicity *in vivo* and is taken up by the organism and thus does not cure the above discussed deficiencies in Xing and the Pentapharm catalogs. In view of the above discussion, applicants request that this rejection be withdrawn.

Claims 6-7 and 13-14 were rejected under 35 USC §103(a) as unpatentable over Xing in view of Pentapharm 1998 or Pentapharm 1997 further in view of Medenica. Medenica was cited for the disclosure of a multichemotherapeutic drug regime. Medenica does not suggest or disclose that Nα(2,4,6-Triisopropylphenylsulfonyl)-3-amidino-(D,L)-phenylalanine 4-ethoxycarbonylpiperazide has efficacy *in vivo*, has no cytotoxicity *in vivo* and is taken up by the organism and thus does not cure the above discussed deficiencies in Xing and the Pentapharm catalogs. In view of the above discussion, applicants request that this rejection be withdrawn.

Claims 16-17 were rejected under 35 USC §103(a) as obvious over Xing in view of Pentapharm 1997 or 1998 further in view of Bicher. Bicher is cited for the disclosure of surgery in combination with chemotherapeutic treatments for

the treatment of cancer. Bicher does not suggest or disclose that Nα(2,4,6-Triisopropylphenylsulfonyl)-3-amidino-(D,L)-phenylalanine 4-ethoxycarbonylpiperazide has efficacy *in vivo*, has no cytotoxicity *in vivo* and is taken up by the organism and thus does not cure the above discussed deficiencies in Xing and the Pentapharm catalogs. In view of the above discussion, applicants request that this rejection be withdrawn.

Claim 10 was rejected on the ground of nonstatutory obviousness-type double patenting as unpatentable over claim 3 of U.S. Patent No. 6,680,320 and claims 11-15 were rejected on the ground of nonstatutory obviousness-type double patenting as unpatentable over claim 3 of U.S. Patent No. 6,680,320 in view of the teachings of U.S. Patent No. 5,736,129. A terminal disclaimer is attached which should overcome these rejections.

Claims 1, 8, 18 and 19 were rejected on the ground of nonstatutory obviousness-type double patenting as unpatentable over claims 8-9 of U.S. Patent No. 6,624,169. A terminal disclaimer is attached which should overcome this rejection.

Applicants respectfully submit that all of claims 1-19 are now in condition for allowance. If it is believed that the application is not in condition for allowance, it is respectfully requested that the undersigned attorney be contacted at the telephone number below.

In the event this paper is not considered to be timely filed, the Applicant respectfully petitions for an appropriate extension of time. Any fee for such an extension together with any additional fees that may be due with respect to this paper, may be charged to Counsel's Deposit Account No. 02-2135.

Respectfully submitted,

By _____

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